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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,079	MONIA ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, and 5-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to a telephone interview held with Jane Massey Licata on June 21, 2004.

Claims 3 and 4 have been canceled.

Claims 1, 2, and 5-18 are pending in the instant application.

Claims 1, 2, and 5-18 have been examined on the merits.

Election/Restrictions

Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the sequences recited in claims 3 and 4 are subject to restriction. The Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of nucleotide sequences to be claimed in a single application. Under this policy, up to 10 of independent and distinct nucleotide sequences will be examined in a single application. (see MPEP 803.04 and 2434).

Claims 3 and 4 specifically claim any one of SEQ ID NOs: 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 45, 46, or 47, directed to antisense compounds targeted to MEKK1. The instant sequences are considered to be unrelated, since each sequence claimed is structurally and functionally independent and distinct for the following reasons: each sequence has a unique nucleotide sequence and each sequence is structurally distinct. Furthermore, a search of more than one (1) of the sequences claimed presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed sequences. Further, because a separate search would be required for each one of the

sequences of claims 13 and 4, restriction for examination purposes as indicated is proper. In view of the foregoing, one (1) sequence is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one (1) sequence from SEQ ID NOs: 2, , 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27. 28, 29, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 45, 46, or 47, of claims 3 and 4.

This is not a species requirement, but a restriction of distinct and independent inventions: unique and structurally distinct nucleotide sequences. Applicant is required to elect one SEQ ID NO. as recited in claims 3 and 4.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

In a telephone conversation with Jane Massey Licata on June 21, 2004, the Attorney requested that the Examiner cancel claims 3 and 4 to expedite prosecution of the instant application.

Claims 3 and 4 have been canceled.

Claims 1, 2, and 5-18 are pending in the instant application.

Claims 1, 2, and 5-18 have been examined on the merits.

Information Disclosure Statement

The information disclosure statement filed on January 18, 2002 is acknowledged. The references referred to therein have been considered on the merits.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2 and 5-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,168,950 ('950). Although the conflicting claims are not identical, they are not patentably distinct from each other because the antisense compounds of claims 1-12 and 14-22 of ('950), targeted to antisense compounds encoding human MEKK1 and modifications of said antisense compounds overlap in scope with the claimed antisense oligonucleotides targeted to a nucleic acid molecule encoding human MEKK1 and modifications of said antisense compounds of the instant invention. The claimed antisense oligonucleotides of the instant invention encompass the issued antisense compounds encoding human MEKK1 of ('950). Further the method of inhibiting the expression of human MEKK1 in human cells or tissues comprising contacting said cells or

tissues *in vitro* with an antisense compound 8 to 30 nucleobases in length targeted to nucleobases 13-464 or nucleobases 2402-3060 of a coding region, or nucleobase 4512-4687 of a 3'-untranslated region of a nucleic acid molecule encoding human MEKK1 of claims 13 and 23 of ('950) overlaps in scope with the method of inhibiting the expression of MEKK1 in human cells or tissues comprising contacting said cells or tissues with an antisense oligonucleotide targeted to a nucleic acid molecule encoding MEKK1 of the instant invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 5-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1, 2, and 5-14 read on compounds of 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human MEKK1, wherein said compound specifically hybridizes with and inhibits the expression of MEKK1. Claims 15-18 read on a method of inhibiting the expression of MEKK1 in human cells or tissues comprising the administration of a compound of 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding MEKK1, wherein said compound specifically hybridizes with and inhibits the expression of MEKK1

The claimed invention encompasses any nucleic acid compound that specifically hybridize to any form of the human MEKK1 gene, which includes mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of human MEKK1 gene (see SEQ ID NO:1).

The specification provides only antisense compounds complementary to target sites of the human MEKK1 mRNA molecule (SEQ ID NO:1), wherein such antisense compounds are effective to inhibit expression of the target sequence (see Tables 1 and 2). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO.1 to predict the structures of antisense compounds complementary to target sites of MEKK1 isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting"

such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of complementary nucleic acid molecules that target human MEKK1, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *in vitro* (cell culture) inhibition of MEKK1 in cells or tissues using antisense targeted to MEKK1, does not reasonably provide enablement for *in vivo* (whole organism) inhibition of MEKK1 in cells or tissues using antisense targeted to MEKK1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claims 15-18 are drawn broadly to inhibition of the expression of MEKK1 in any cell *in vivo* (whole organism) for the treatment of any disease that is associated with MEKK1, including a hyperproliferative disorder or cancer, using antisense targeted to a nucleic acid encoding MEKK1.

The specification provides examples wherein phosphorothioate and chimeric phosphorothioate antisense targeted to a nucleic acid encoding MEKK1 inhibited the expression of MEKK1 *in vitro* (cell culture) in human cell lines (see Tables 1 and 2). The specification does not demonstrate any correlation with the inhibition of MEKK1 in cell culture and a treatment effect for any disease or condition associated with MEKK1. The Specification does not present any examples wherein antisense targeted to MEKK1 was delivered to cells *in vivo* (whole

organism), nor wherein antisense targeted to MEKK1 inhibited the expression of MEKK1 in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including a hyperproliferative disorder or cancer.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was highly unpredictable due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81), Branch (TIBS, 1998 Vol. 23:45-50 and Jen et al. (Stem Cells, 2000 Vol. 18:307-319)). Such obstacles include, for example, problems with delivery, target accessibility, and the potential for unpredictable nonantisense effects. Jen et al. state, "One of the major limitations for the therapeutic use of AS-ODNSs and ribozymes is the problem of delivery... Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable" (see page 313, second column, second paragraph). Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive" (see page 315, second column). Branch addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are

particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, as claimed. The specification provides examples wherein antisense oligonucleotides targeted to MEKK1 are delivered to cells *in vitro* and the expression of MEKK1 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences, and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (Molecular Medicine Today, 2000, Vol. 6:72-81) (see page 79 and 80, section entitled *Cellular uptake facilitators for in vitro studies*) states, "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides... *In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide". Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to

MEKK1 to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific cells or tissues to target with MEKK1 oligonucleotides and how to specifically deliver oligonucleotides to an organism *in vivo* (whole organism) at a concentration effective to result in the inhibition of the expression of MEKK1. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the oligonucleotide molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment, and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 12, 13, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Sivaraman et al. [U.S. Patent No. 6,271,210].

Claim 1 is drawn to an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human MEKK1, wherein said antisense compound specifically hybridizes with and inhibits the expression of human MEKK1. Claims 2, 12, 13, and 14 are depend on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense compound is an antisense oligonucletoide, wherein the antisense compound comprises a pharmaceutically acceptable carrier or diluent and further comprises a colloidal dispersion system.

Sivaraman et al. disclose an antisense oligonucletoide with the following sequence: 5'-gccgccgccgccgccau-3' (see (Sivaraman et al. SEQ ID NO:3). This antisense oligonucletoide is reverse complementary to bases 112-124 of human MEKK1 (SEQ ID NO:1) of the instant invention. Although the antisense oligonucleotide disclosed by Sivaraman et al. is targeted to the

ERK gene, the antisense oligonucletoide meets all the structural requirements of the instant claims and would also be expected to specifically hybridize to a nucleic acid encoding human MEKK1, as per applicant's definition set forth in the specification as filed, pages 5 and 6, lines 9-35 and 1-2, respectively. Furthermore, since the prior art antisense oligonucletoide meets all the structural limitations of the claims, the prior art antisense oligonucletoide would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary.

Therefore Sivaraman et al. anticipate claims 1, 2, 12, 13, and 14.

Claims 1, 2, and 5-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. [U.S. Patent No. 6,335,194].

Claims 1, 2, 12, 13, and 14 have been described above. Claims 4-11 depend on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucletoide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claim 14 is drawn to a method of inhibiting the expression of MEKK1 in human cells or tissues comprising contacting said cells or tissues with an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human MEKK1, so that expression of MEKK1 is inhibited.

Bennett et al. disclose an antisense oligonucletoide with the following sequence: 5'-catgccgccgccgccacc-3' (see Bennett et al. SEQ ID NO:99). This antisense oligonucletoide is reverse complementary to bases 112-125 of human MEKK1 (SEQ ID NO:1) of the instant invention. Although the antisense oligonucleotide disclosed by Bennett et al. is targeted to the survivin gene, the antisense oligonucletoide meets all the structural requirements of the instant claims and would also be expected to specifically hybridize to a nucleic acid encoding human MEKK1, as per applicant's definition set forth in the specification as filed, pages 5 and 6, lines 9-35 and 1-2, respectively. Furthermore, since the prior art antisense oligonucletoide meets all the structural limitations of the claims, the prior art antisense oligonucletoide would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. Bennett et al. further disclose that the antisense oligonucletoide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide (see Bennett et al. columns 6-8). Bennett et al. also disclose method of inhibiting the expression of survivin in human cells or tissues *in vitro* comprising contacting said cells or tissues with an antisense compound targeted to a nucleic acid molecule encoding survivin, so that expression of survivin is inhibited (see Table 1). Although the disclosed method uses an antisense compound targeted to the survivin gene, the antisense oligonucleotide meets all the structural limitations of

the claims, the prior art antisense oligonucletoide would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary

Therefore, Bennett et al. anticipate claims 1, 2, and 5-14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 5-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (Genes and Development, 1998 Vol. 12:3369-3381) in view Mercola et al. [WO 98/54203], and Baracchini et al. (U.S. Patent No. 5,801,154).

Claims 1, 2, and 5-18 are drawn to an antisense oligonucleotide 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding MEKK1; wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase;

wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising an antisense oligonucleotide 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding MEKK1 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of MEKK1 in cells *in vitro*.

Xia et al. teaches the full-length sequence of human MEKK1 as represented in SEQ ID NO:1 of the instant invention (see Xia et al. at page 3370, second column). Xia et al. do not teach antisense targeted to MEKK1, including antisense with a length of 8 to 30 nucleobases. Xia et al. also do not teach antisense targeted to a nucleic acid encoding MEKK1 wherein the antisense comprises modified internucleoside linkages or wherein the antisense is a chimeric antisense molecule.

Mercola et al. suggest making MEKK1 inhibitors, including ribozymes, antisense nucleic acids, or dominant negative mutants of MEKK1. Mercola et al. do not teach antisense targeted to MEKK1, including antisense with a length of 8 to 30 nucleobases. Mercola et al. also do not teach antisense targeted to a nucleic acid encoding MEKK1 wherein the antisense comprises modified internucleoside linkages or wherein the antisense is a chimeric antisense molecule.

Baracchini et al. teach antisense of 8 to 30 nucleobases in length and teach modifications to antisense, including 2'-O'methoxyethyl sugar modifications, 5-methylcytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity (see for example columns 6-9). Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art to make an antisense oligonucletoide targeted to a nucleic acid encoding MEKK1 using the sequence taught by Xia and the motivation of Mercola et al. It would have been obvious to make a length within the range of 8 to 30 nucleobases (as taught by Baracchini et al.) because antisense of a short length are more easily synthesized and easier to deliver to cells. It would have been further obvious to make said antisense comprising modifications, including 2'-O'methoxyethyl sugar modifications, 5-methylcytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages as taught by Baracchini et al, because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule, (see for example, Baracchini et al. column 6, paragraph 3).

It would have been obvious to one of ordinary skill in the art to make an antisense compound comprising antisense targeted to MEKK1 and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al. Further, it would have been obvious to make an antisense compound targeted to MEKK1 because Mercola et al. teach generally making inhibitors to MEKK1, and teach the specific embodiment of antisense nucleic acids, and Xia et al. taught a human MEKK1 encoded by a nucleic acid comprising human MEKK1 of the instant invention.

One skilled in the art would have been motivated to make an antisense molecule targeted to a nucleic acid encoding MEKK1 because Mercola et al. explicitly teaches inhibiting the

expression of MEKK1 using antisense nucleic acids and it is well known in the art that antisense is a means by which a target protein can be specifically targeted for functional studies and Xia et al. teach human MEKK1 as a protein to be studied and teach the full length sequence of a nucleic acid encoding human MEKK1. One of ordinary skill in the art would be motivated to make such antisense of a length within the rang of 8 to 30 nucleotides for ease of synthesis and delivery and because it is conventional in the art to make antisense within this size range (as exemplified by Baracchini et al.). One of ordinary sill would have been motivated to incorporate the modifications taught by Baracchini et al. into an antisense molecule targeted to MEKK1, for the benefits of stability and improved hybridization.

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding MEKK1 in a method of inhibiting the expression of MEKK1 in cells *in vitro* (cell culture) because Mercola et al. suggest using antisense targeted to MEKK1 to inhibit the expression of MEKK1 in cells *in vitro*, and it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding human MEKK1.

Therefore, the invention of claims 1, 2, and 5-18 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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